BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Application Number: 10/781,254
Filing Date: February 18, 2004
Appellant: Joel E. Bernstein

APPEAL BRIEF

Honorable Director of Patents and Trademarks
PO Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This appeal is from the Examiner's final Office Action mailed May 16, 2008 in which all pending claims (namely, claims 1-7, 11 and 12) were rejected. A telephonic interview was held on August 20, 2008. A timely Notice of Appeal was filed November 17, 2008 with the required fee.

This brief is being filed along with the required $540 fee pursuant to 37 CFR §41.20(b)(2) that should be deducted from Deposit Account No. 12-0913.

(i) Real Party in Interest

This application is assigned to Gideon Pharmaceuticals, Inc.

The Assignment is recorded at Reel 02011, Frame 0743.

(ii) Related Appeals and Interferences

There are no known related appeals or interferences which have any relation to this appeal.

(iii) Status of Claims

Fourteen claims (1-14) were filed. In response to a restriction, Group I, claims 1-7, 11 and 12 to a composition comprising a preponderance of cis doxepin isomer over trans doxepin isomer, was elected.

Group II, claims 8-10, 13 and 14 to a method of treating affective, painful or allergic disorder comprising treatment with a composition containing a preponderance of cis doxepin isomer over trans doxepin isomer, were withdrawn.

(iv) Status of Amendments

A Final Rejection was mailed May 16, 2008. A telephone interview was held August 26, 2008.

The amendment filed September 24, 2008 was entered in the Advisory Action of December 29, 2008. Claims as set forth in the Claims Appendix are currently on appeal.

(v) Summary of Claimed Subject Matter[1]

Claim 1

Claim 1 relates to a composition having a preponderance of cis doxepin isomer over trans doxepin isomer. [0004] The doxepin isomer is present in an amount of about 0.01% to about 10.0% by weight, and a pharmaceutically acceptable vehicle. [0004] The composition is used in the treatment of affective, painful, allergic disorders. [0003]

[1] Support is indicated by numbers of paragraphs in the specification.

The composition is comparable in efficacy to compositions containing a preponderance of the trans doxepin isomer, but has significantly less sedative effects. [0003]

Claim 2

Dependent claim 2 relates a composition suitable for application to the skin. [0004]

Claim 3

Dependent claim 3 relates to a composition including a vehicle selected from the group consisting of a lotion, a solution, a cream, an ointment, a gel, or a paste. [0004]

Claim 4

Dependent claim 4 relates to a composition suitable for application to mucous membranes. [0004]

Claim 5

Dependent claim 5 relates to a composition with a vehicle selected from the group consisting of solutions, suspensions, suppositories, and plasticized formulations. [0004]

Claim 6

Dependent claim 6 relates to a composition suitable for injection. [0004]

Claim 7

Dependent claim 7 relates to a composition wherein cis doxepin isomer is present in the amount of about 0.05% to about 5.0% by weight. [0004]

Dependent claims 8-10 are withdrawn.

Claim 11

Claim 11 relates to a composition suitable for oral administration. [0005] The composition includes a pharmaceutically acceptable vehicle in the form of capsules, tablets, liquid solutions or suspensions and contains a preponderance of cis doxepin isomer over trans doxepin isomer. [0005] The cis doxepin isomer may be present in an amount of about 0.5-500.0 mg per capsule, tablet or 5 ml portion of liquid. [0005] The composition is comparable in efficacy to compositions containing preponderance of the trans doxepin isomer, but with significantly less sedative side effects. [0005]

Claim 12

Dependent claim 12 relates to cis doxepin isomer present in the amount of about 1.0-50.0 mg per capsule, tablet, or 5 ml portion of liquid. [0005]

Claims 13 and dependent claim 14 are withdrawn.

(vi) Grounds of Rejection To Be Reviewed on Appeal

There is only one rejection at issue, whether claims are obvious over a publication by Midha.[2] [35 USC §103(a)].

(vii) Argument

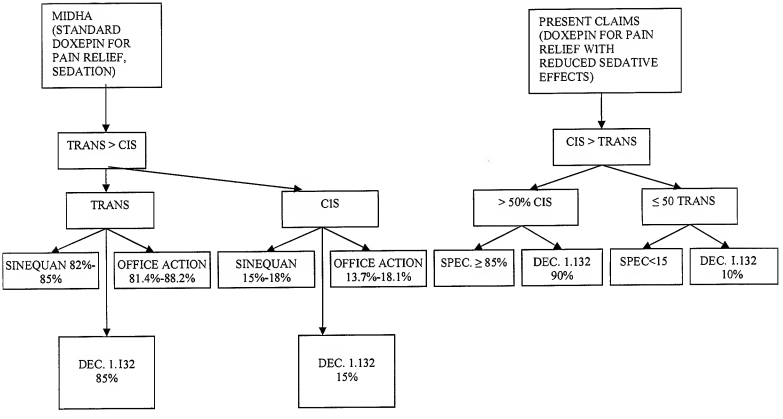
Claims are not obvious because (1) the Midha publication does not teach those of skill in the art to use a preponderance of cis doxepin isomer over trans, (2) the examiner failed to specifically refute a Declaration under 37 CFR 1.132 further showing surprising and unexpected results, and (3) the goal of less sedation must be considered in analyzing composition claims for obviousness.

[2] Midha, K.K. (1992) Eur. J.Clin. Pharmacol, pp. 539-544.

A. The Midha Publication Does Not Teach Those of Skill in the Art to Use a Preponderance of Cis Doxepin Isomer over Trans

There is no disagreement between the examiner and appellant about what is expressly taught in the art about the relative proportions of trans:cis isomers in doxepin used for pain relief. (See FIG. 1)

FIG. 1 MIDHA TEACHES DIRECTLY OPPOSITE THE PROPORTION OF TRANS:CIS ISOMERS IN DOXEPIN THAN CLAIMED



SPEC. = SPECIFICATION
DEC. = DECLARATION

On pages 3 and 4 of an Office Action dated October 9, 2007, the Examiner noted that

> ...doxepin hydrochloride U.S.P is a geometric isomer mixture" containing not less than 13.7% and not more than 18.1% of the cis isomer and "not less than 81.4% and not more than 88.2% of the trans isomer. (specification, page 1, lines 14-18.) Applicants also admit that the systemic side effects (i.e., sedation) of doxepin occur in from 20% to over 60%..., (*sic re placement of quotation marks)*

The examiner admits that a "preponderance" of cis over trans isomers in a doxepin composition is a difference from the art, but said the composition claimed with a preponderance of cis was obvious

> because cis-doxepin is more **active** than trans as disclosed by Midha et al. (*emphasis provided*)

Office Action, October 9, 2007, p. 4.

Midha used the "standard" formulation of doxepin (15-18% cis, 82-85% trans), known as SINEQUAN and described as a "sedating drug"(RX List, the Internet Drug Index). Midha measured a metabolite of doxepin, and did not offer conclusions from the reported study on cis versus trans isomer of doxepin activity, nor on sedation.

In the Advisory Action, the examiner admits that Midha only cites to a publication by Pinder et al. in the Background of the Midha paper, for comments on "cis" versus "trans". Both Midha and Pinder only relate animal work, no human results.

"Preponderance" is a term in the specification. [0007] [0003] Also "any trans doxepin isomer that may be present in an amount less than that of the cis doxepin isomer [0004] [0005] The Midha publication, the sole support for the remaining 35 U.S.C. §103 rejection, does not include any data teaching elements of the rejected claims. This publication does not teach a composition with a preponderance of cis. The examiner bases her rejection not on a publication or combination of publications that teaches claims 1-7 and 11-12, but only on a phrase in Midha, page 539,

> the cis-isomer may be the more active

then the trans isomer) a phrase not based on work of Midha, but on a citation to Pinder (which teaches away) from the claimed compound.

With regard to obviousness, appellant argues that Midha, which only relates Pinder's comments that cis is more active than trans, coupled with U.S. Pat. 5,502,047 that reports doxepin, which is predominantly trans isomer, is used to treat insomnia, does not make the claimed invention obvious. If the examiner's assumption that cis is expected to be more active than trans for sedation, then these 2 publications considered together would teach away from a preponderance of cis, because the prediction would be a **greater** degree of sedation, not less as disclosed in the application and Declaration under 37 CFR 1.132.

The activity for which Midha cites Pinder [[1] Pinder et al. – *Drugs* 13; 161-218 (1977)] is an activity to increase sedation (Pinder, page 169); which teaches away from the claimed composition, which provides less sedation and moreover in the Pinder reference, sometimes the cis is more active and sometimes trans is more active, depending upon the biochemical effect examined.

The examiner's conclusion is not based on work by Midha, but is only supported by a cite to Pinder et al. in the Background of Midha's paper.

> ...although animal studies suggest that the cis-isomer may be the more active [1].

In fact, Pinder reviews the confusing results of animal studies on doxepin effects, as illustrated by the following:

Pinder citation

p166 cis more active than trans in antagonizing reserpine-induced hypothermia in mice (Schaumann & Rebbentrop 1966). Another study showed cis and trans have equivalent activity in the same model. (Otsuki et al. 1972).

p167 "Most of the activity of doxepin in this test appeared to reside in the *trans*-isomer, which comprises 85% of the commercially available drug; for the *cis* isomer was virtually ineffective." Trans was much more active in inhibiting 5HT uptake. Cis was virtually ineffective (Buczko et al 1974).

p168 cis slightly more potent than trans at inhibiting avoidance behavior.

p168 cis enhanced amphetamine-induced hyperactivity whereas trans antagonized the hyperactivity; cis more potent than trans in inhibiting conditioned avoidance behavior (Otsuki et al 1972b).

p169 the cis isomer is more active in potentiating urethane-induced sedation (Schumann & Ribbentrop 1966), and cis is more potent than trans in hexobarbital-induced sleep in mice (Otsuki et al 1972).

p170 cis more potent than trans inhibiting acetylcholine-induced spasm in guinea pig ileum.

p171 cis & trans are **equivalent** in producing dose-related decrease in blood pressure in dogs.

(per Table 2 on p 250 of Ross) the cis is **more active** than the trans in some respects and **less active** than the trans in others.

The examiner added U.S. Pat. 5,502,047 ('047) of record, which in fact has as its goal, deliberate sedation. The novelty is said to be administering lower dosages as compared to the art of higher doses of psychotherapeutic agents which have sedation as a side effect. Low doses were not taught in the art, and unexpected sedation effects without other side effects of high or moderate dosages, were reported.

This patent, referred to by the examiner, extensively defines "dosage" as the amount of the compound administered (in the Background, Summary and Detailed Description of the Invention). '047 does not refer to components of any compound nor are isomers of doxepin mentioned. However, the doxepin used is SINEQUAN RTM marketed by Pfizer, Inc. This doxepin had 82-85% trans compound to 15-18% cis (see FIG. 1).

Stereoisomers have the same molecular formula or atomic composition, but different spatial arrangements. The terms "cis" and "trans" refer to the relative spatial arrangements of constituents "cis" on the same side of a plane, "trans" on opposite sides.

No scientific principle or teaching in the art has been set forth by the examiner to predict differences in function of the cis versus trans isomers in different combinations. The examiner relies solely on a secondary reference in Midha to Pinder that cis isomer doxepin is "more active."

But the in the Advisory Action the examiner now switches to the term "**potent**" instead of "active."

> cis-isomer is more **potent** than trans-isomer disclosed by Midha as published by Pinder et al. (*emphasis provided*)

The examiner's further reasoning in support of maintaining the obviousness rejection is still unfounded:

> This teaching would motivate one of ordinary skill in the art to formulate preponderance of cis-isomer of doxepin over trans-isomer in order to formulate more **potent** composition of doxepin ...
>
> One would have been motivated to employ the composition comprising substantially more of cis isomer than trans isomer of doxepin to achieve at least comparable or superior benefit in the treatment of affective disorder therapy. The degree of desired sedation is obvious because as admitted by the Appellant that sedation of doxepin depends upon dosage and the route of doxepin administration as well known in the art by Appellant's admission.

Office Action May 16, 2008, page 6.

Here, the examiner is equating "dosage" with the claimed composition components. "Dosage" would not be interpreted by those of skill in the art to refer to the percentages of isomers in the total compositions. "Dosage" is well known to refer to

> **Dosage.** The giving of medicine or other therapeutic agent in prescribed amounts.
>
> **Dose.** The quantity of a drug or other remedy to be taken or applied all at one time or in fractional amounts without a given period.

Stedman's Medical Dictionary, 27th Edition, 1999, pp. 537, 1433.

Midha relates a single dose.

A basis for the continuing disagreements is that the examiner equates, without any support, her finding "that the cis-isomer is more **active** than the trans isomer," with a **"preponderance"** of cis, concluding therefore that, although she admits a preponderance of cis is **not** reported in the art, those of skill would somehow find it obvious to use a **preponderance** of cis isomer because it was **more active** than trans.

There is no citation from the examiner to support that those of skill in the art were looking for better **pain relief** than provided by the standard of doxepin. Indeed the present composition is equivalent to the standard in that aspect. Despite her conclusion that doxepin (transisomer preponderant) is known as a sedative in the art, she speculates that those of skill would be motivated to flip flop the proportion of trans over cis isomers in the art, to favor cis because cis might be **"more active"**. If this means more sedation, and cis is "**more active,**" no explanation is provided why one of skill in the art use more, rather than less cis-isomer doxepin if a goal was to reduce sedation.

The examiner argues that one would put more cis in just because it is alleged by more active, but there is no indication those of skill in the art would tamper with an approved and - for pain relief- satisfactory formula.

Case law supports the unpredictability of structure and function of different isomers.

A recent Federal Circuit case, *Sanofi,* cited *In re May*, 574 F.2d 1082, 1090, 197 USPQ 601 (CCPA 1978) the novelty of an optical isomer is not negated by the prior art disclosure of its racemate" and continued

> The knowledge that enantiomers may be separated is not "anticipation" of a specific enantiomer that has not been separated, identified, and characterized. We discern no error in the district court's findings that, on the state of the prior art, a person of ordinary skill would not have had the expectation that separating the enantiomers would be likely to produce an isomer having absolute stereoselectivity as to both the favorable antiplatelet activity and the unfavorable neurotoxicity.

Sanofi Synthelabo v. Apotex 550 F.3d 1075, 1090, 89 USPQ2d (BNA) 1370, (Fed. Cir. 2008).

In *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263 (Fed. Cir. 2007), the court recognized the known difficulty of separating enantiomers and the unpredictability of their properties, and held that a reference that stated that a compound has enantiomers did not enable the separation of those enantiomers, where the reference did not teach how to obtain the enantiomer. *Id.* at 1268-69.

Therefore, the biological functions of isomers are unpredictable, so just relating cis and trans isomer doxepins in the art does not anticipate or make the present claims obvious.

B. The Examiner Failed to Address a Declaration Under 37 CFR 1.132

A personal interview was held at the U.S. Patent and trademark Office, January 9, 2008. Appellant's inventor explained "preponderance" and offered a Declaration to support "surprising and unexpected results."

A Declaration under 37 CFR 1.132 was submitted to support surprising and unexpected effects. Comparative investigative data was presented on rats and human patients.

(a) Single oral doses of doxepin (90% cis/10% trans) showed virtually no sedation compared to rats receiving doxepin (85% trans/15% cis) at the same dosage, and

(b) Patients in need thereof received doxepin with trans isomer 85%, a wash out, and then doxepin with cis isomer 90%. Pain relief was equal in the 2 groups, but all patients reported sedation with the trans predominant, and almost all of the predominantly cis group reported no sedation.

The examiner discounted the Declaration under 37 CFR 1.132 as evidence of surprising and unexpected results explaining only because

> the "evidence" of surprising and unexpected results is not commensurate in scope with the breadth of the claims.

The examiner did not explain why the evidence did not match the claim scope. Just as appellants and their representatives are precluded from making conclusory statements without support, so must the examiner justify ignoring a Declaration under oath, without presenting any discussion of why nothing in the Declaration was considered persuasive. There is **no showing at all** of results not being "commensurate in scope with the breadth of the claims sought to be patented." (Advisory Action)

In a case cited by the examiner, the appellant just recognized an advantage of something existing in the art. In the present case, appellant created a different composition. The examiner's case support is misplaced (5/16/08, p. 6). In *Obiaya*, the

claims related to the parallel flow of a divided sample to two different analyzers, a vacuum to draw the sample to the analyzers and then to exhaust, and a heater means. *Ex parte Obiaya*, 227 USPQ 58, 59 (Bd. Pat. App. & Inter. 1985). The patent appellant indicated that an advantage could be obtained by using a labyrinth heater. *Id.* The court, however, found that simply noticing the advantage was not an unexpected result because the references disclosing labyrinth heaters sufficiently suggested such advantage. *Id* Unlike the references in *Obiaya*, in the present appeal, no reference suggests selecting the components in the claimed composition, nor the advantageous result that the inventor achieved by deliberately making cis preponderant over the art, directly opposite to compositions in the art. No reference suggested a preponderance of the "cis-isomer." Therefore, Obiaya does not support the examiner's arguments.

In *Greenfield*, the patent appellant claimed a pain composition covering a subgenus having hundreds of compounds. *In re Greenfield*, 571 F.2d 1185, 1189, 197 USPQ 227, 230 (CCPA 1978). The Appellant provided evidence of unexpected results using one particular compound. *Id.* The court found that the unexpected results proved by using one compound was not sufficient to prove that a subgenus of hundreds of compounds would obtain the same result. *Id.* Similarly in *Lindner*, the patent appellant presented test results of only one mixture of ingredients while claiming a mixture covering a broader scope of numerous compounds. *In re Lindner* 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972). In *Kulling*, the claims simply did not cover the compounds that appellant used to obtain the unexpected result. *In re Kulling* 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990).

In contrast to these fact situations, in the present case, sufficient evidence of unexpected results is presented. Unlike *Greenfield*, *Lindner* and *Kulling*, the compositions for which the unexpected results are presented fall within the scope of the compositions in the claims. Therefore, evidence of unexpected results covered the full scope of the claims.

C. The Goal of Less Sedation Must be Considered in Analyzing Composition Claims for Obviousness

The claims are directed to pharmaceutical compositions comprising a preponderance of cis doxepin isomer over trans doxepin isomer. Indeed, a surprising

and unexpected finding is that this composition has significantly less sedative effects than the compositions used previously, a preponderance of trans doxepin isomer. Less sedative efforts are desirable when treating affective, painful, allergic disorders.

> Principal among the systemic side effects accompanying doxepin administration, and most limiting to its usefulness as a drug, is sedation which occurs in from 20% to over 60% of subjects depending upon dosage and route of doxepin administration.

Specification, par [0002]

The efficacy of the composition, however, is comparable to compositions containing a preponderance of the trans doximer isomer which has undesirable sedation effects. "Efficacy" refers to pain relief, and "active" refers to that function, id. Midha (Summary) cited by the examiner.

No art or combination of art in pain medications has been cited teaching a composition with a preponderance of cis doxepin. In fact in the art, the trans doxepin isomer is always predominant in compositions. Midha also confirms this.

As argued in the record, the publication referred to by Midha relating that cis is more "active" teaches away from using more of it in a composition invented to **reduce** sedation, assuming for the sake of the examiner's argument that activity is related to sedation. Although the examiner argues that a goal of the invention (motivation), that is, to reduce sedation while maintaining equivalent pain relief, is irrelevant in determining non-obviousness of composition claims, the fact remains that pharmaceutical compositions are formulas directed to achieve certain effects. Those of skill in the art would not make the present composition in a vacuum. Teachings in the art would be relevant based on **effects**. Pharmaceutical compositions are not result of recipes out of the blue.

The examiner argues that the claims are to compositions, not methods, therefore the examiner argues the goal to reduce sedative effects by using a preponderance of cis-doxepin isomer, a composition not found anywhere in the art by the examiner, is not relevant to argue against obviousness. Yet, the examiner uses the stated goal as the basis for her obviousness rejection.

The examiner argues:

> The motivation to combine need not be Appellant's motivation to invent.

citing *In re Dillon*, 16 USPQ2d 1897 (Fed. Cir. 1990), Advisory Action, December 29, 2008.

The Board indeed found obviousness even though no reference disclosed the use applicant discovered, but in *Dillon* compositions were recited that were merely "analogous to those in prior patents," and applicant made "no showing to overcome prima facie presumption of similar properties for those analogous compositions." This is not the factual situation in the present case where appellant provides evidence that the prior art does not have analogous properties regarding reduced sedation. In fact, the standard doxepin is accompanied by warnings that sedation is a risk. Also in contrast to the facts in *Dillon,* cis isomers were shown to be superior to trans. In *Dillon*

> She did not present any showing of data to the effect that her compositions had properties not possessed by the prior art compositions or that they possessed them to an unexpectedly greater degree. She attempted to refute the significance of the teachings of the prior art references. She did not succeed and we do not believe the PTO was in error in its decision.

Id at 1902.

The present invention was not a "discovery" of a new use of a known compound. The present invention is a **new composition** not reported previously for treatment of humans. In contrast to the composition claims in *Dillon*, the present composition is "physically or structurally distinguishable from those of prior art patents..", which the court said may not be obvious. *Id* at 1901.

Requirements for obviousness rejections are not met in the examiner's arguments. The examiner has not shown any composition of cis greater than trans in the art of treating humans with doxepin, nor has she provided any "motivation to combine" from the art.

"To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the

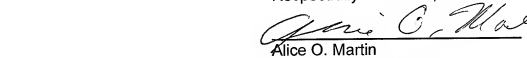
artisan would have found the claimed invention to have been obvious in light of the teachings of the references." MPEP § 706.02(j) *quoting Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). A determination of obviousness requires that "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved." *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 1734, 82 USPQ2d 1385 (2007), *quoting Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). In making a determination of obviousness by looking at the teachings of multiple patents, one should consider

> the effects of demands known to the design community or present in the market place; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *To facilitate review, this analysis should be made explicit.*

KSR, 127 S.Ct. at 1740-41 (*emphasis added*). "[A] patent composed of several elements is not proved obvious merely by demonstrating the each of its elements was, independently, known in the prior art." *Id.* at 1741. In the present case, Midha does not even teach all the claimed elements.

Reversal of the Examiner is therefore clearly in order and is solicited.

Respectfully submitted,



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(viii) Claims Appendix

1. A composition comprising a preponderance of cis doxepin isomer over trans doxepin isomer, said cis doxepin isomer being present in an amount of about 0.01% to about 10.0% by weight, and a pharmaceutically acceptable vehicle, said composition for use in the treatment of affective, painful, allergic disorders, said composition being comparable in efficacy to compositions containing a preponderance of the trans doxepin isomer but with significantly less sedative effects.
2. The composition of claim 1 wherein said composition is suitable for application to the skin.
3. The composition of claim 2 wherein said vehicle is selected from the group consisting of a lotion, a solution, a cream, an ointment, a gel, or a paste.
4. The composition of claim 1 wherein said composition is suitable for application to mucous membranes.
5. The composition of claim 4 wherein said vehicle is selected from the group consisting of solutions, suspensions, suppositories, and plasticized formulations.
6. The composition of claim 1 wherein said composition is suitable for injection.
7. The composition of claim 1 wherein said cis doxepin isomer is present in the amount of about 0.05% to about 5.0% by weight.
8. (Withdrawn) A method of treating affective, painful or allergic disorders comprising treatment with an effective amount of a composition containing a preponderance of cis doxepin isomer over trans doxepin isomer, said cis doxepin isomer being present in an amount of about 0.01% to about 10.0% by weight in a pharmaceutically acceptable vehicle, said composition being comparable in efficacy to compositions containing a preponderance of the trans doxepin isomer but with significantly less sedation.
9. (Withdrawn) The method of claim 8 wherein said method of treatment is selected from the group consisting of application to skin, application to mucous membranes and injection.
10. (Withdrawn) The method of claim 8 wherein said cis doxepin isomer is present in the amount of about 0.05-5.0% by weight.

11. A composition suitable for oral administration comprising a pharmaceutically acceptable vehicle in the form of capsules, tablets, liquid solutions or suspensions and containing a preponderance of cis doxepin isomer over trans doxepin isomer, said cis doxepin isomer present in an amount of about 0.5-500.0 mg per capsule, tablet or 5 ml portion of liquid, said composition being comparable in efficacy to compositions containing a preponderance of the trans doxepin isomer but with significantly less sedative side effects.

12. The composition of claim 11 wherein said cis doxepin isomer is present in the amount of about 1.0-50.0 mg per capsule, tablet, or 5 ml portion of liquid.

13. (Withdrawn) A method of treating affective, painful, or allergic disorders by oral administration and comprising treatment with an effective amount of a composition containing a preponderance of cis doxepin isomer over trans doxepin isomer, said cis doxepin isomer being present in an amount of about 0.5-500.0 mg per dose or 5 ml portion of liquid in a pharmaceutically acceptable vehicle, said composition being comparable in efficacy to compositions containing a preponderance of trans doxepin isomer but with significantly less sedative side effects.

14. (Withdrawn) The method of claim 13 wherein said cis doxepin isomer is present in the amount of about 1.0-50.0 mg per dose.

(ix) Evidence Appendix

Declaration under 37 CFR 1.132

Ex parte Obiaya, 227 USPQ 58, 59 (Bd. Pat. App. & Inter. 1985)

Forest Laboratories, Inc., Forest Laboratories Holding, Ltd., and H. Lundbeck A/S v. Ivax Pharmaceuticals, Inc. and CIPLA, Ltd., 501 F.3d 1263, 84 USPQ2d 1099 (2007)

Graham v. John Deere Co., 383 U.S. 1, 17 (1966)

In re Dillon, 16 USPQ2d 1897 (Fed. Cir. 1990)

In re Greenfield, 571 F.2d 1185, 1189, 197 USPQ 227, 230 (CCAP 1978)

KSR International Co. v. Teleflex, Inc., 550 U.S., 398, 127 S.Ct. 1727, 1734, 82 USPQ2d 1385 (2007)

In re Kulling 897 F.2d 1147, 1149, 14 USPQ2d 1056, 1058 (Fed. Cir. 1990)

In re Lindner 457 F.2d 506, 508, 173 USPQ 356, 358 (CCPA 1972)

R.M. Pinder et al., *Doxepin Up-to-Date: A Review of its Pharmacological Properties and Therapeutic Efficacy with Particular Reference to Depression*, ADIS Press pp. 161-218 (1977)

Sanofi Synthelabo v. Apotex 550 F.3d 1075, 1090, 89 USPQ2d (BNA) 1370, (Fed. Cir. 2008)

Stedman's Medical Dictionary, 27th Edition, (1999), p. 537, 1433.

K.K. Midha, Eur. J. Clin Pharmacol *Stereoselective Pharamacokinetics of Doxepin Isomers* (1992) pp. 539-544.

U.S. Pat. No. 5,502,047

Related Proceedings Appendix

None.